PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference -/-	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/005004	International filing date *(day/month/year)* 26.11.2004	Priority date *(day/month/year)* 26.11.2003
International Patent Classification (IPC) or national classification and IPC C07D471/04, A61K31/437		
Applicant THE UNIVERSITY COURT OF THE UNIVERSITY... et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 24 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.09.2005	01.03.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Baston, E Telephone No. +49 89 2399-8229

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/005004

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 2, 5-20, 23-98	as originally filed
3, 4, 21, 22	received on 16.09.2005 with letter of 13.09.2005

Claims, Numbers

1-42	received on 16.09.2005 with letter of 13.09.2005

Drawings, Sheets

1/4-4/4	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27 "with respect to industrial applicability"

because:

☒ the said international application, or the said claims Nos. 27 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-42
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-29,35,39-41
	No:	Claims	30-34,36-38,42
Industrial applicability (IA)	Yes:	Claims	1-26,28-42
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

To section III

Claim 27 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

To section V

The following documents were cited in the search report and were considered for the examination of the present application:

D2: LYNCH, M.A. ET AL.: "Synthesis, Biological Activity and Comparative Analysis of DNA Binding Affinities and Human DNA Topoisomerase I Inhibitory Activities of Novel 12-Alkoxy-benzo[c]phenanthridinium Salts" BIOORGANIC&MEDICINAL CHEMISTRY LETTERS, vol. 11, 2001, pages 2643-2646,

D3: WHITTAKER, J. ET AL.: "The interaction of DNA-targeted platinum phenanthridinium complexes with DNA" NUCLEIC ACIDS RESEARCH, vol. 26, 1998, pages 3933-3939,

D4: WO 96/03384 A (CTRC RESEARCH FOUNDATION) 8 February 1996

The present application is directed to phenanthridinium derivatives which are considered to be useful for the treatment of e.g. cancer due to DNA binding properties.
The compounds according to general formula A (claim 1) are characterized by the fact that R_2,R_3 and R_4,R_5 are either forming an aromatic or hetaromatic ring or are selected from an aromatic substituent.
Claims 7 and 9 are directed to precursor compounds according to formulae B and Bii.

The most relevant documents of the prior art D2 and D3 only relate to phenanthridinium compounds (also with affinity for DNA), which do not have any further heteroring condensed. Thus the requirements of Art. 33(2) PCT are met for claims 1-40.
Moreover none of these documents provides an indication for the claimed structures and the description (pages 47-53) reveals cytotoxity data for select congeners according to formula A. Thus the involvement of an inventive step is acknowledged (claims 1-26,35,39-41) for compounds according to claim 1, related precursors used in the preparation of

these compounds and preparation procedures. Also uses with respect to anti-cancer treatment are considered to meet the requirements of Art. 33(3) PCT.

Claims 30-34, 36-38 and 42 are not considered to involve an inventive step (Art. 33(3) PCT) for the following reasons:
Claims 30 and 31 also encompass uses like "photochemically active agent" or "phase transfer catalyst" etc. without any evidence in the description. Only data with respect to cytotoxic properties are presented, thus rendering only a potential use for cancer credible.

Claim 32 (and dependent claims) extend the scope for the methods of synthesizing to any heterocyclic aromatic cationic compound without limitation for structures according to claim 1. Thus the majority of structures falling under the scope of claim 32 cannot be prepared by the claimed process.

Additionally the problem of unity of invention (Rule 13.1 PCT) could become important, since the inventive concept for the method of synthesising is inevitably associated with the attribution of an inventive step for the prepared compounds. For those parts of claim 32 which do not assist in the preparation of compounds of formula A a different inventive concept would then have to be developed which is a priori different from the one of claim 1.

All functional definitions in claim 27 ("DNA cross-linking agent" or "DNA binding agent") have to be replaced by well defined diseases (Art. 6 PCT). It is considered that the affinity for DNA is a mechanism of action underlying a potential use as an anti-cancer agent, which itself is only of scientific value but cannot constitute subject-matter to be claimed.

For the assessment of the present claim 27 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

To section VI

D1: PARENTY, A.D. ET AL.: "General One-Pot, Three-Step Methodology Leading to an Extended Class of N-Heterocyclic Cations: Spontaneous Nucleophilic Addition, Cyclization, and Hydride Loss" JOURNAL OF ORGANIC CHEMISTRY, vol. 69, 8 June 2004 (2004-06-08), pages 5934-5946,

The priority document of the present application is not yet available. In case that the presently claimed subject matter is not fully supported by the priority document, D1 will be relevant for the assessment of novelty in the national / European phase.

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Summary of the Invention

Broadly, the present invention concerns new classes of heterocyclic aromatic cationic compounds, and in particular new classes of phenanthridinium derivatives, most notably dihydro-imidazo-phenanthridinium (DIP) compounds. These findings are based on the reaction of the middle b ring of a phenanthridinium core with primary amines to form DIP compounds (Formula A) or secondary amines to form 2-aminoalkyl phenanthridinium derivatives (Formula B). These reactions can also be applied to other classes of starting compounds which comprise a 6-membered ring aromatic heterocycle having a ring nitrogen and at least one alpha hydrogen atom which can be reacted with a primary or secondary amine.

Moreover, analogous reactions can be carried to produce dihydro-thiazoles, e.g. by reaction with a ~~sulphate~~ sulphide such as sodium ~~sulphate~~ sulphide Na_2S, and to produce dihydro-oxazoles, e.g. by reaction with a hydroxide such as KOH.

Typically, the chemistry disclosed herein has the advantage that is amenable to scaling up to large scale production as it does not involve any particularly hazardous reaction procedures. Further, the one pot reactions disclosed herein are usually carried out at room temperature and usually take less than 12 hours, with the result that the energetic cost of the industrialization process may be quite low.

In general, N-based heteroaromatic cations are highly interesting compounds due to their reactivity and biological properties. For instance, molecules containing a phenanthridinium core are one important subset of heteroaromatic cations with applications as drugs

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(topoisomerase inhibitors and DNA targeting agents), dyes and probes due to their high affinity for DNA. Moreover, a simple purification method (i.e. filtration of the reaction medium and wash) may make them very good candidates for combinatorial chemistry. Finally, because of the highly effective hydride transfer of the intermediaries in forming the phenanthridinium derivatives, there may be applications in non-enzymatic redox transformation, e.g. the reduction of ketones, sulfonatates, arenediazoniums and aldehydes.

A first class of compounds represented herein by Formula A are based on the ring extension of the heteroaromatic middle **b** ring of the phenanthridinium core, typically forming a new 5-8 membered ring, and more preferably a five or six membered ring. The new ring may comprise a dihydro-imidazolium, a dihydro-thiazolium, a dihydro-oxazolium moiety or a tetrahydro-pyrimidinium moiety, depending on whether the reaction is carried out with a primary amines or a ~~sulphate~~ sulphide or hydroxide compound to introduce a nitrogen, a sulphur or an oxygen heteroatom respectively. A second class of compounds represented by Formula B are based on the reaction of the heteroaromatic middle b ring of the phenanthridinium core with secondary amines, followed by an intramolecular rearrangement process.

In other aspects, the present invention provides methods for synthesising the compounds of the invention. The inventors have also elucidated the mechanisms of these reactions which are unprecedented. The mechanisms provide a basis for extending the specific reaction described herein to the synthesis of other types of heterocyclic aromatic cationic compounds.

preferably, the pH of the reaction is less that about 10, and more preferably is less than about 9.

For primary amines, this second method B is much more advantageous than the first one. Nevertheless, the first Method A is generally preferred for the formation of dimers, trimers and multimers because, for solubility reasons, DMF is more appropriate. Method A is also better for the formation of [5-(2-amino-alkyl)-phenanthridiniums *via* the use of secondary amines.

Accordingly, the synthetic methods disclosed herein provide a strategy for the synthesis of the compounds of the invention. In the syntheses illustrated herein, the reaction of a primary amine is used to produce derivatives of [2,3-dihydro-1*H*-imidazo [1,2-*f*] phenanthridin-4-ylium bromide] or the reaction of a secondary amine is used to produce derivatives of [5-(2-amino-ethyl)-phenanthridinium. However, the reactions disclosed herein are general and can be extended to other heterocyclic aromatic moieties containing a ring nitrogen and at least one adjacent alpha hydrogen. Furthermore, the reactions are extremely easy to perform as isolating a pure final product simply requires a filtration and a washing procedure to afford product in high yield.

Accordingly, in a further aspect, the present invention provides a method of synthesising a heterocyclic aromatic cationic compound with an additional ring, the method comprising reacting a heterocyclic aromatic cationic compound comprising a ring nitrogen and at least one alpha hydrogen atom with a substituted or unsubstituted primary amine, a ~~sulphate~~ sulphide or a hydroxide, wherein the primary amine, ~~sulphate~~ sulphide or hydroxide reacts with the heterocylic

aromatic compound by alpha addition, cyclisation and an oxidation step thereby providing the heterocyclic aromatic compound with an additional ring. In preferred embodiments, the ring produced in this reaction is five membered. In a preferred embodiment, the heterocyclic aromatic starting material is the 2-bromo-ethyl-phenanthridinium, which reacts with a primary amine to yield a 2,3-Dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide derivative.

The method can be used for the production of 5 and 6-membered rings and to produce thiazole and oxazoles as well as phenanthridinium compounds by using a ~~sulphate~~ sulphide or a hydroxide respectively. The Methods A and B described herein are particularly advantageous as they involve an addition and a cyclisation followed by an aromatisation process that involves one equivalent of the starting material as an oxidizing agent (Method A) or a external oxidizing agent like NBS (Method B). In preferred embodiments, this has the particular advantage that the reaction can proceed in one pot. While the application of this new chemistry to the production of phenanthridinium compounds in which the b ring is extended is preferred, the reaction is equally applicable to the extension of other heteroaromatic compounds such as quinolines, isoquinolines, quinazolines or pyridines.

In one embodiment, the method is for making a compound represented by Formula A and comprises:

reacting a heterocyclic aromatic compound represented by the Formula A':

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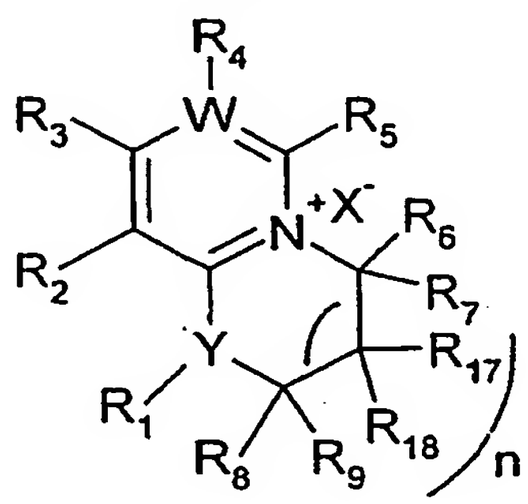
Claims:

1. A compound represented by Formula A:



wherein:

n = 0, 1, 2 or 3 such that:

when n = 0, the substituents R_{17} and R_{18} and the carbon atom to which they are bonded are not present; and

when n is 1, 2 or 3, the substituents R_{17} and R_{18} present on the respective carbon atom(s) may be the same or different and are independently selected from hydrogen or a substituent;

W is C or N, such that when W is N, R_4 is a lone pair of electrons;

Y is selected from N, O or S, such that:

when Y is O or S, R_1 is a lone pair of electrons; or

when Y is N, R_1 is selected from hydrogen, unsubstituted or substituted C_{1-7}alkyl, unsubstituted or substituted C_{1-7}cycloalkyl, unsubstituted or substituted C_{1-7}cycloalkyl-C_{1-7}alkyl, unsubstituted or substituted C_{5-20}aryl, unsubstituted or substituted C_{5-20}aryl-C_{1-7}alkyl, unsubstituted or substituted C_{3-20}heterocyclyl, or a linking group to form a multimeric compound in which a plurality of compounds represented by Formula A are covalently bonded together;

independently R_2 and R_3 and/or R_4 and R_5 together ~~can~~ form an aromatic carbon or heterocyclic ring structure,

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optionally substituted with one or more aromatic substituents, or R_2, R_3, R_4 and R_5 are independently selected from an aromatic substituent;

R_6 and R_7 are independently selected from hydrogen or independently or together can be a substituent;

R_8 and R_9 are independently selected from hydrogen or independently or together can be a substituent;

wherein when R_{17} and R_{18} are present, they are independently selected from hydrogen or independently or together can be a substituent; and

one of the substituents R_6 and R_7 which is present on the carbon atom at the alpha position to the aromatic ring may form a double bond with one of the substituents R_8 and R_9 or R_{17} and R_{18} which is present on the carbon atom at the beta position to the aromatic ring; and

X^- is an anionic moiety;

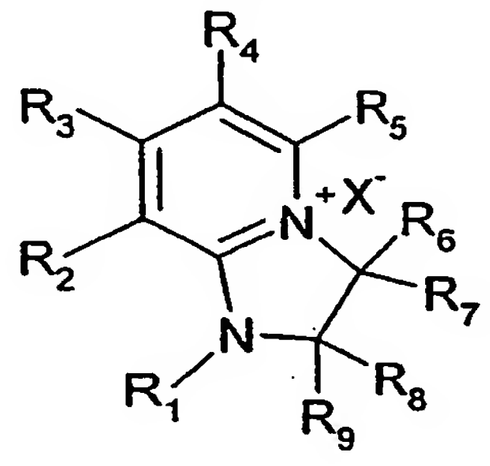
and wherein:

the substituent or substituents are independently selected from halo, hydroxy, oxo, ether, formyl, C_{1-7}alkylacyl, C_{5-20}arylacyl, acylhalide, carboxy, ester, acyloxy, amido, acylamido, thioamido, tetrazolyl, amino, nitro, nitroso, azido, cyano, isocyano, cyanato, isocyanato, thiocyano, isothiocyano, sulfhydryl, thioether, sulfonic acid, sulfonate, sulfone, sulfonyloxy, sulfinyloxy, sulfamino, sulfonamino, sulfinamino, sulfamyl, sulfonamido, C_{1-7}alkyl, C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, C_{5-20}aryl-C_{1-7}alkyl, C_{3-20}heterocyclyl, or

C_{5-20}aryl; and

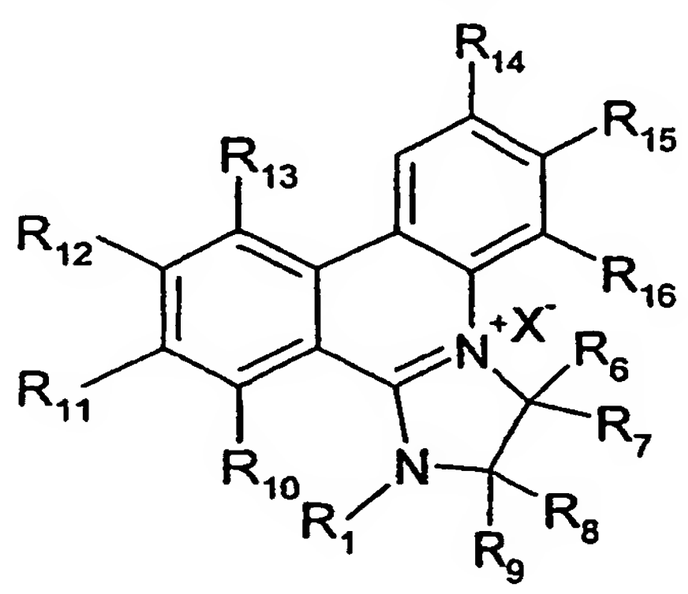
the aromatic substituent or substituents are independently selected from hydrogen, -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -SH, -SMe, -SEt, -C(=O)Me, -C(=O)OH, -C(=O)OMe, $-CONH_2$, -CONHMe, $-NH_2$, $-NMe_2$, $-NEt_2$, $-N(nPr)_2$, $-N(iPr)_2$, -CN, $-NO_2$, -Me, -Et, $-CF_3$, $-OCF_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, -Ph, ether, ester, amido, amino, C_{1-7}alkyl, C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, or C_{5-20}aryl-C_{1-7}alkyl.

2. The compound according to claim 1, wherein the compound is represented by Formula Ai:



wherein the substituents are as defined in claim 1.

3. The compound according to claim 1 or claim 2, wherein the compound represented by Formula Aii:



wherein the R_1, R_6, R_7, R_8 and R_9 substituents are as defined in claim 1 and R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} substituents are independently selected an aromatic substituent.

4. The compound according to any one of the preceding claims, wherein R_1 is a substituted C_{1-7}alkyl group selected from substituted C_{1-7}alkyl, C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, or C_{1-7}aminoalkyl.

5. The compound according to any one of the preceding claims, wherein R_1 is a selected from C_{5-20}aryl, C_{5-20}carboaryl, C_{5-20}heteroaryl, C_{1-7}alkyl-C_{5-20}aryl or C_{5-20}haloaryl, optionally substituted with one or more substituents.

6. The compounds according to any one of the preceding claims which is:

1-(4-Methoxy-benzyl)-2,3-dihydro-1*H*-imidazo[1,2-*f*]phenanthridinium bromide;

1-(2-Hydroxy-ethyl)-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

2,3-Dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-Isopropyl-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-Cyclopropyl-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-(4-Methoxy-phenyl)-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-Phenyl-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-paramethoxyaniline-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-Methoxycarbonylmethyl-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-(1-Methoxycarbonyl-2-phenyl-ethyl)-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-Benzyl-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-(2-Mercapto-ethyl)-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

3-(4-Methoxy-benzyl)-2,3-dihydro-1H-imidazo[1,2-a]quinolin-10-ylium bromide;

1-(4-Methoxy-benzyl)-2,3-dihydro-1H-imidazo[2,1-a]isoquinolin-4-ylium bromide;

1-(4-Methoxy-benzyl)-2,3-dihydro-1H-imidazo[1,2-a]pyridin-4-ylium bromide; 1-Propyl-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-(2-Hydroxy-1-methyl-ethyl)-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-[1-(4-Methoxy-phenyl)-ethyl]-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

7-Bromo-1-(4-methoxy-benzyl)-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-(4-Ethyl-phenyl)-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-Hexyl-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-Dodecyl-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-Octadecyl-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide;

1-(3,3-Diphenyl-propyl)-2,3-dihydro-1H-imidazo[1,2-f]phenanthridin-4-ylium bromide; or

1-(4-Methoxy-benzyl)-2,3-dihydro-1H-imidazo[1,2-c]quinazolin-4-ylium bromide.

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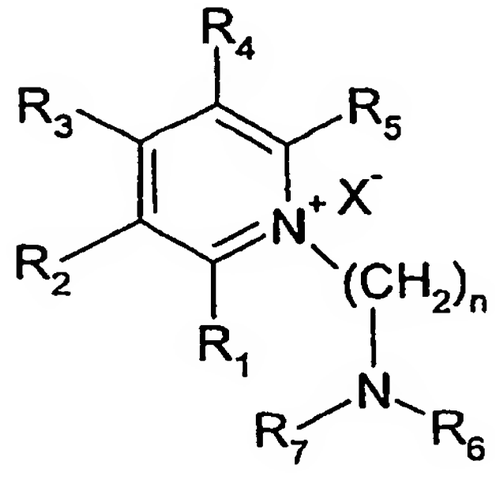
7. A compound represented by Formula B:



wherein:

n is 2 to 5;

R_1 is hydrogen;

independently R_2 and R_3 and/or R_4 and R_5 together can form an aromatic carbon or heterocyclic ring structure, optionally substituted with one or more aromatic substituents, or R_2, R_3, R_4 and R_5 are independently selected from an aromatic substituent;

R_6 and R_7 are independently a substituent or a linking group to form a multimeric compound in which a plurality of compounds represented by Formula A as set out in any one of claims 1 to 7 and/or Formula B are covalently bonded together;

X^- is an anionic moiety;

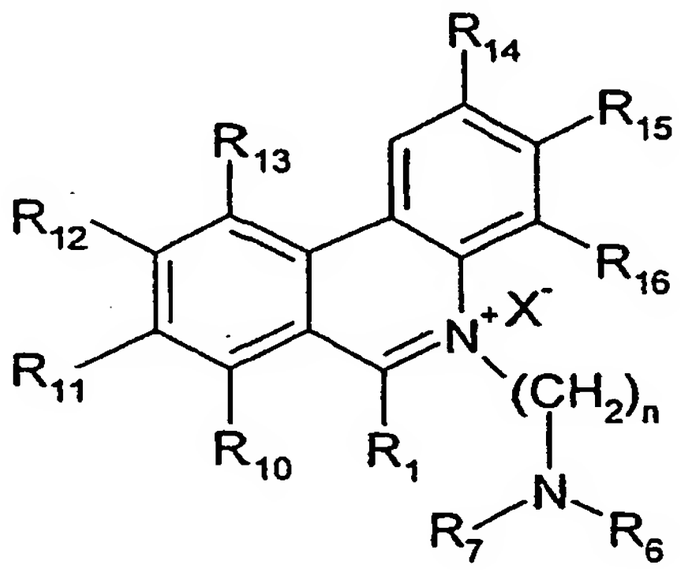
and wherein:

the substituent or substituents are independently selected from halo, hydroxy, oxo, ether, formyl, C_{1-7}alkylacyl, C_{5-20}arylacyl, acylhalide, carboxy, ester, acyloxy, amido, acylamido, thioamido, tetrazolyl, amino, nitro, nitroso, azido, cyano, isocyano, cyanato, isocyanato, thiocyano,

isothiocyano, sulfhydryl, thioether, sulfonic acid, sulfonate, sulfone, sulfonyloxy, sulfinyloxy, sulfamino, sulfonamino, sulfinamino, sulfamyl, sulfonamido, C_{1-7}alkyl, C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, C_{5-20}aryl-C_{1-7}alkyl, C_{3-20}heterocyclyl, or C_{5-20}aryl; and

the aromatic substituent or substituents are independently selected from hydrogen, -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -SH, -SMe, -SEt, -C(=O)Me, -C(=O)OH, -C(=O)OMe, $-CONH_2$, -CONHMe, $-NH_2$, $-NMe_2$, $-NEt_2$, $-N(nPr)_2$, $-N(iPr)_2$, -CN, $-NO_2$, -Me, -Et, $-CF_3$, $-OCF_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, -Ph, ether, ester, amido, amino, C_{1-7}alkyl, C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, or C_{5-20}aryl-C_{1-7}alkyl.

8. The compound according to claim 7 which is represented by Formula Bi:



wherein:

n is 2 to 5;

R_1 is hydrogen;

R_6 and R_7 are independently hydrogen, a substituent or a linking group to form a multimeric compound in which a

plurality of compounds represented by Formula A and/or Formula B are covalently bonded together;

R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are independently selected from hydrogen or an aromatic substituent; and

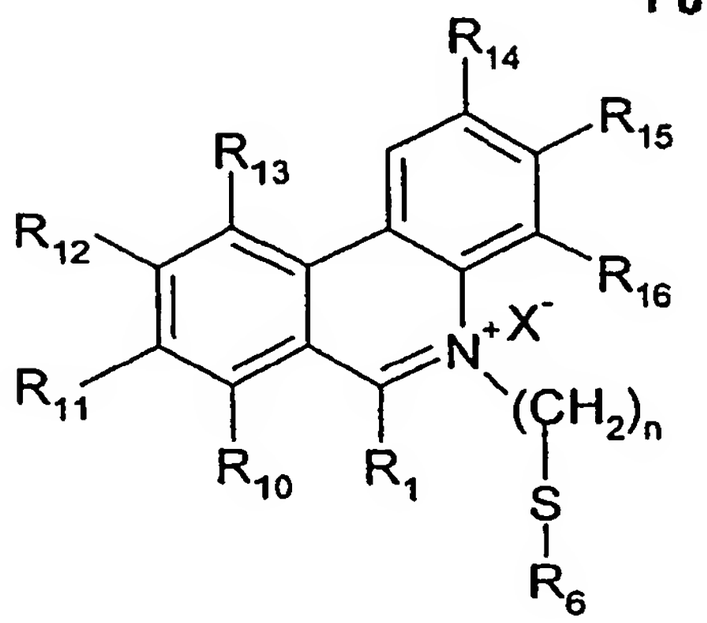
X^- is an anionic moiety

and wherein:

the substituent or substituents are independently selected from halo, hydroxy, oxo, ether, formyl, C_{1-7}alkylacyl, C_{5-20}arylacyl, acylhalide, carboxy, ester, acyloxy, amido, acylamido, thioamido, tetrazolyl, amino, nitro, nitroso, azido, cyano, isocyano, cyanato, isocyanato, thiocyano, isothiocyano, sulfhydryl, thioether, sulfonic acid, sulfonate, sulfone, sulfonyloxy, sulfinyloxy, sulfamino, sulfonamino, sulfinamino, sulfamyl, sulfonamido, C_{1-7}alkyl, C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, C_{5-20}aryl-C_{1-7}alkyl, C_{3-20}heterocyclyl, or C_{5-20}aryl; and

the aromatic substituent or substituents are independently selected from hydrogen, -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -SH, -SMe, -SEt, -C(=O)Me, -C(=O)OH, -C(=O)OMe, $-CONH_2$, -CONHMe, $-NH_2$, $-NMe_2$, $-NEt_2$, $-N(nPr)_2$, $-N(iPr)_2$, -CN, $-NO_2$, -Me, -Et, $-CF_3$, $-OCF_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, -Ph, ether, ester, amido, amino, C_{1-7}alkyl, C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, or C_{5-20}aryl-C_{1-7}alkyl.

9. A compound which is represented by the Formula Bii:



wherein:

n is 2 to 5;

R_1 is hydrogen;

R_6 is hydrogen, a substituent; or a linking group to form a multimeric compound in which a plurality of compounds represented by Formula A and/or Formula B are covalently bonded together;

R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are independently selected from hydrogen or an aromatic substituent; and

X^- is an anionic moiety

and wherein:

the substituent or substituents are independently selected from halo, hydroxy, oxo, ether, formyl, C_{1-7}alkylacyl, C_{5-20}arylacyl, acylhalide, carboxy, ester, acyloxy, amido, acylamido, thioamido, tetrazolyl, amino, nitro, nitroso, azido, cyano, isocyano, cyanato, isocyanato, thiocyano, isothiocyano, sulfhydryl, thioether, sulfonic acid, sulfonate, sulfone, sulfonyloxy, sulfinyloxy, sulfamino, sulfonamino, sulfinamino, sulfamyl, sulfonamido, C_{1-7}alkyl,

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C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, C_{5-20}aryl-C_{1-7}alkyl, C_{3-20}heterocyclyl, or C_{5-20}aryl; and

the aromatic substituent or substituents are independently selected from hydrogen, -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -SH, -SMe, -SEt, -C(=O)Me, -C(=O)OH, -C(=O)OMe, $-CONH_2$, -CONHMe, $-NH_2$, $-NMe_2$, $-NEt_2$, $-N(nPr)_2$, $-N(iPr)_2$, -CN, $-NO_2$, -Me, -Et, $-CF_3$, $-OCF_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, -Ph, ether, ester, amido, amino, C_{1-7}alkyl, C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, or C_{5-20}aryl-C_{1-7}alkyl.

10. The compound according to any one of claims 7 to 9, wherein n is 2 or 3.

11. The compound according to any one of claims 7 to 10, which is::

5-(2-tert-butylamino-ethyl)-phenanthridinium bromide;
5-(2-Piperidin-1-yl-ethyl)-phenanthridinium bromide;
piperazine phenanthridinium derivatives;
hydroxylamine derivatives;
1,5,9triaza-Cyclododecane;
5-[2-(4-methoxy-benzylsulfanyl)-ethyl]-phenanthridinium bromide.

12. The compound according to any one of the preceding claims, wherein X^- the anionic moiety is selected from halogen, tosylate or mesylate.

13. The compound according to any one of the preceding claims, wherein when the R_2 and R_3 and/or R_4 and R_5 substituents are present, one or both of these pairs of substituents together form an aromatic carbon or

heterocyclic ring structure, optionally substituted with one or more aromatic substituents.

14. The compound according to any one of the preceding claims, wherein the compounds forming the multimeric compound are covalently bonded together via their respective R_1 substituents (Formula A) or via their R_6 or R_7 substituents (Formula B) or via a spacer group.

15. A multimeric compound formed by covalently linking two or more of the same or different compounds according to any one of the preceding claims

16. The multimeric compound according to claim 15, wherein compounds of Formula A are linked via the R_1 substituent and/or compounds represented by Formula B are linked via the R_6 and/or R_7 substituents.

17. The multimeric compound according to claim 15 or claim 16, wherein, where the compounds of Formula B are linked via the R_6 and R_7 substituents, the resulting linkage forms a cycloalkyl group.

18. The multimeric compound according to any one of claims 15 to 17, wherein the compounds are covalently bonded via a linker group or linker groups.

19. The multimeric compound according to claim 18, wherein the linker groups is a C_{1-7} alk-di-yl group bonded to another group of Formula A or B in place of R_1 thereof; a piperazin-di-yl group bonded to another group of Formula A or B in place of R_1 thereof; a (N,N-C_{1-6} dialkylene) C_{1-7} alkylene amine bonded to two other groups of Formula A or B in place of R_1 thereof; or a cyclo (C_{4-8}) alk-tri-yl

group bonded to two other groups of Formula A or B in place of R_3 thereof.

20. The multimeric compound according to any one of claims 15 to 17, wherein the multimeric compound is a dimer, trimer or tetramer of the compounds according to any one of claims 1 to 14.

21. The multimeric compound according to any one of claims ~~13~~ 15 to ~~18~~ 20, wherein the compounds of Formula A and/or B are covalently bonded to a spacer group.

22. The multimeric compound according to claim ~~19~~ 21 in which 2 or more, 3 or more, 4 or more, 5 or more, 10 or more, 20 or more, 50 or more, or 100 or more compounds represented by Formula A or B are covalently linked via one or more spacer groups.

23. The multimeric compound according to claim ~~19~~ 21 or claim ~~20~~ 22, wherein the spacer group is a polyamine compound comprising an alkyl chain having a plurality of amine groups for reacting with the compounds of Formula A an/or B.

24. The multimeric compound according to any one of claim 15 to ~~21~~ 23, wherein the compound is a selected from:

Dimers:

Ethylene diamine derivative with two groups of Formula A.

Hydroxylamine derivative with two groups of Formula B.

Piperazine derivative with two groups of Formula B.

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DIP dimer derived from the spacer N1-(2-Amino-ethyl)-ethane-1,2-diamine

DIP dimer derived from the spacer 2-Amino-1-[4-(2-amino-acetyl)-piperazin-1-yl]-ethanone

DIP dimer derived from the spacer 2-[4-(2-Amino-ethyl)-piperazin-1-yl]-ethylamine

Phenanthridinium dimer derived from the spacer 2-[4-(2-Amino-ethyl)-piperazin-1-yl]-ethylamine

Trimers:

Tris (2-aminoethylamine) derivatives with three groups of Formula A

Cis-triaminocyclohexane derivatives with three groups of Formula A.

2-Amino-1-[5,9-bis-(2-amino-acetyl)-1,5,9triaza-cyclododec-1-yl]-ethanone derivative with three groups of Formula A.

2-[5,9-Bis-(2-amino-ethyl)-1,5,9triaza-cyclododec-1-yl]-ethylamine derivative with three groups of Formula A.

1,5,9-triaza-cyclododecane derivative with three groups of Formula B.

DIP trimer derived from the spacer 2-Amino-1-[5,9-bis-(2-amino-acetyl)-1,5,9triaza-cyclododec-1-yl]-ethanone

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DIP trimer derived from the spacer Cyclohexane-1,3,5-triamine

Phenanthridinium trimer derived from the spacer 2-[5,9-Bis-(2-amino-ethyl)-1,5,9triaza-cyclododec-1-yl]-ethylamine

Tetramers:

Tetrakis-(6-amino-hexyl)-ammonium bromide derivative with four groups of Formula A.

25. A composition comprising one or more compounds according to any one of the preceding claims.

26. A compound according to any one of claims 1 to ~~22~~ 24 for use in a method of therapy or diagnosis.

27. Use of a compound according to any one of claims 1 to ~~22~~ 24 as a DNA cross-linking agent, a DNA binding agent, a telomere binding agent, a biological probe or a diagnostic probe.

28. Use of a compound according to any one of claims 1 to ~~22~~ 24 for the preparation of a medicament for the treatment of a condition treatable by an anti-cancer agent, an anti-inflammatory agent, or an antiprotozoal agent, ~~or a topoisomerase inhibitor~~

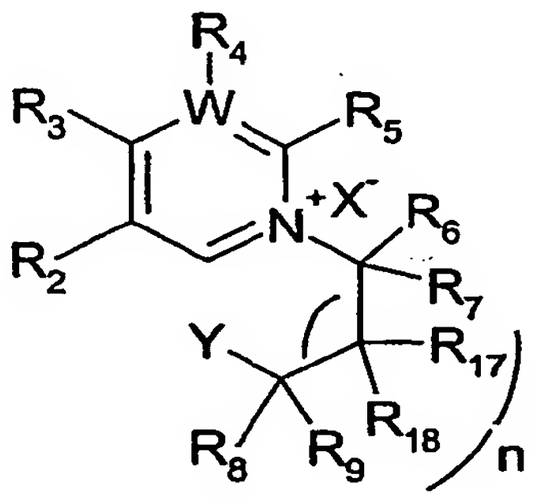
29. The use according to claim ~~26~~ 28, wherein the medicament is for the treatment of cancer.

30. Use of a compound according to any one of claims 1 to ~~22~~ 24 as a synthetic agent, a reducing agent, a chiral

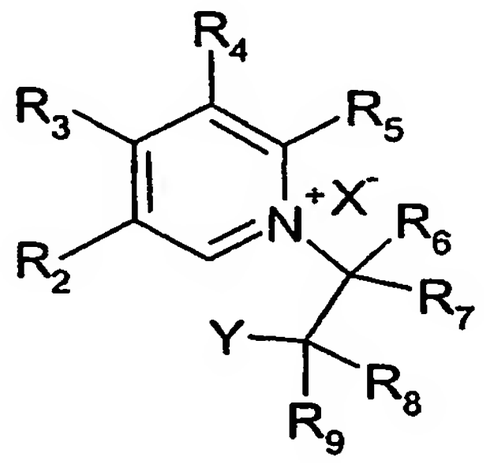
reducing reagent, an amine protecting group, a phase transfer catalyst, or a chiral resolving agent for purification or crystallisation.

31. Use of a compound according to any one of claims 1 to ~~22~~ 24 as an electronic material, a photochemically active agent or sensor or as molecular switching device.

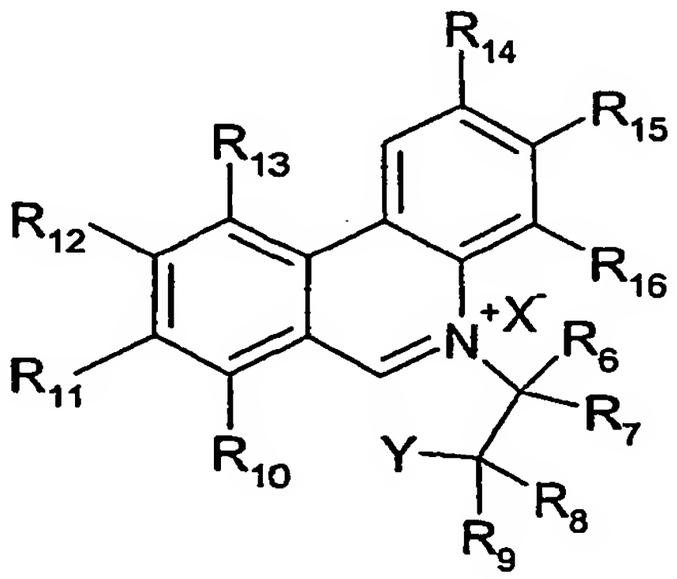
32. A method of synthesising a heterocyclic aromatic cationic compound with an additional ring, the method comprising reacting a heterocyclic aromatic cationic compound comprising a ring nitrogen and at least one alpha hydrogen atom according to formula A', Ai' or Aii'



A'



Ai'



Aii'

with a substituted or unsubstituted primary amine, a ~~sulphate~~ sulphide or a hydroxide, wherein the primary amine, ~~sulphate~~ sulphide or hydroxide reacts with the heterocylic aromatic compound by alpha addition, cyclisation and an

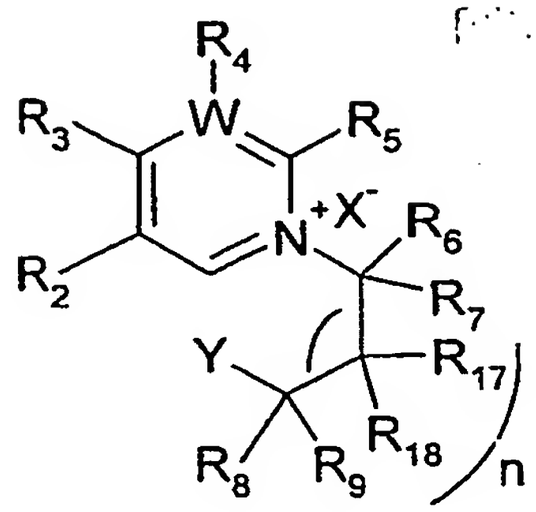
oxidation step thereby providing the heterocyclic aromatic compound with an additional ring.

33. The method according to claim ~~30~~ 32, wherein the additional ring is a five membered ring.

34. The method according to claim ~~30~~ 32 or claim ~~31~~ 33, wherein the reaction is a one pot reaction.

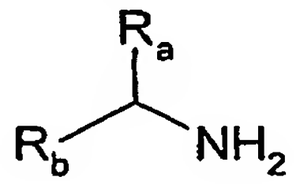
35. The method according to any one of claims ~~30~~ 32 to ~~32~~ 34, wherein the method is for making a compound represented by Formula A as defined in claim 1 and comprises:

reacting a heterocyclic aromatic compound represented by the Formula A':



wherein Y is a leaving group and n and the remaining substituents are as defined in claim 1;

with a primary amine represented by the formula:

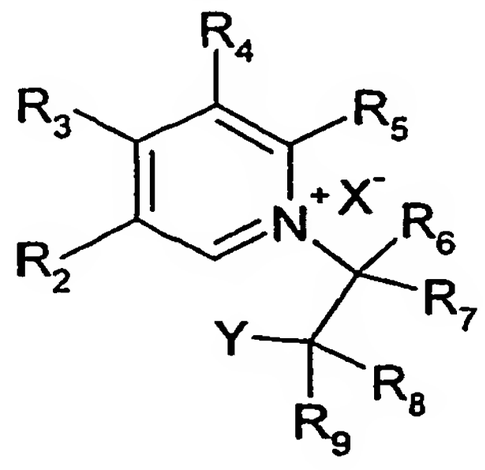


wherein the R_a-C-R_b substituents of the primary amine forms the group R_1 in the final compound;

the primary amine reacting with the phenanthridinium compounds of Formula A' by addition, cyclisation and oxidation to produce a compound represented by Formula A.

36. The method according to any one of claims ~~30~~ 32 to ~~33~~ 35, wherein the method is for making a compound represented by Formula Ai or Aii as defined in claim 2 or claim 3 and comprises:

reacting a heterocyclic aromatic compound represented by the Formula Ai' or Aii' respectively:



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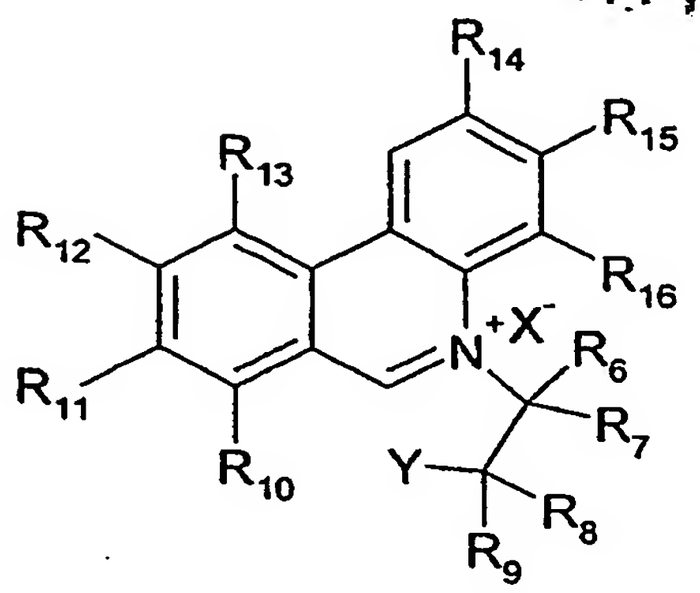
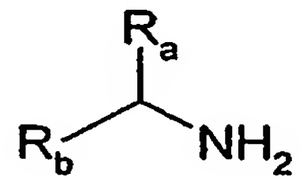


wherein Y is a leaving group and the remaining substituents are as defined in claim 2 or claim 3;

with a primary amine represented by the formula:



wherein the R_a-C-R_b substituents of the primary amine forms the group R_1 in the final compound;

the primary amine reacting with the phenanthridinium compounds of Formula Ai' by addition, cyclisation and oxidation to produce a compound represented by Formula Ai.

37. The method according to any one of claims ~~30~~ 32 to ~~34~~ 36, wherein the method uses a primary amine which (1) has no substituents in the alpha position, or (2) has a primary carbon in the alpha position, or (3) has a secondary carbon in the alpha position), or (4) has a tertiary carbon in the alpha position, or (5) is or derives from an amino acid.

38. The method according to any one of claims ~~30~~ 32 to ~~34~~ 36, wherein the primary amine is an aromatic amines, such as naphthalen-1-ylamine or anthracen-9-ylamine.

39. A method of making compounds represented by Formula B as defined in claim 7, the method comprising:

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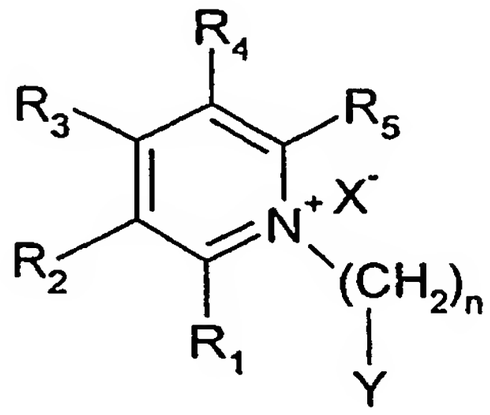
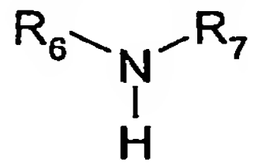
reacting a heterocyclic aromatic compound represented by the Formula B':



wherein Y is a leaving group and the remaining substituents are as defined in claim 7;

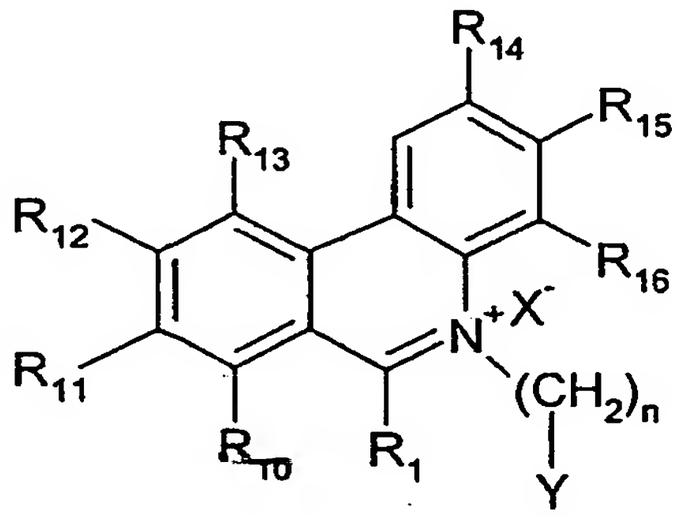
with a secondary amine represented by the Formula:



the secondary amine reacting with the compound of Formula B' to produce a compound represented by Formula B.

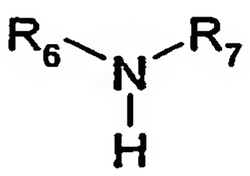
40. The method according to claim 39 for making compounds represented by Formula Bi as defined in claim 8, the method comprising:

reacting a heterocyclic aromatic compound represented by the Formula Bi':



wherein Y is a leaving group and the remaining substituents are as defined in claim 8;

with a secondary amine represented by the formula:



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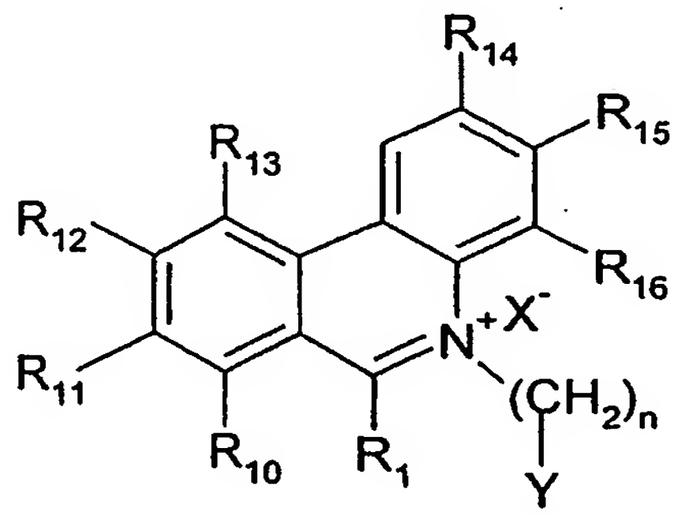
the secondary amine reacting with the compound of Formula Bi' by to produce a compound represented by Formula Bi.

41. A method of making compounds represented by Formula Bii as defined in claim 9, the method comprising:

reacting a heterocyclic aromatic compound represented by the Formula Bii':



with a sulphur containing compound such as substituted or unsubstituted thiol to produce a compound represented by Formula Bii.

42. The method according to any one of claims ~~30~~ 32 to ~~39~~ 41, further comprising the step of forming a multimeric compound according to any one of claim 15 to ~~22~~ 24.